

REMARKS

In the February 21, 2008 Office Action, the Examiner: (1) declined to recognize the claim of priority to certain parent applications; (2) rejected claims 75-76, 78-82, 85, 86, 91-93, 95, 96-98, 102, 106-109, and 112-115 under 35 U.S.C. § 103(a) as being unpatentable over Kimpton *et al.* (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina *et al.* (Biometrics (1980) 36:161-165) and further as motivated in view of Jeanpierre (Ann. Hum. Genet. (1992) 56:325-330); and (3) rejected claims 75-82, 85-87, 91-98, 100, 102, 106-115 under 35 U.S.C. § 103(a) as being unpatentable over Kimpton in view of Ledwina and further as motivated in view of Jeanpierre and further in view of Goelet *et al.*

Applicants have amended claims 75, 81 and 82, and canceled claims 77, 87, 93, 96-98, 100, 102, and 106-115. Claim 75 has been amended to include the limitation of previously pending claim 87 that each allele is defined by a single specific nucleotide and the limitations that the reaction value is the intensity of an allele specific quantitative signal and that the conditional probability is a measure of the likelihood of the genotype given the first reaction value. Support for the new language appears in the specification at Figure 3, showing measures of the intensity of the signal; col. 2, lines 28-29 of parent application US 5,762,876:¹ “differentially labelled [*sic*] dideoxynucleoside triphosphates”; col. 3, lines 49-50: “optical transducer to read reaction results”; col. 3, lines 65 – col. 4, line 9: “‘reaction value’ . . . may refer . . . to a single numerical value or to a collection of numbers associated with a physical state produced by the reaction. . . optical signals are produced that may be read as a single numerical value. . . optical signals generated by GBA or other reaction methods”; col. 5, lines 17-22: “optical detector 11 to produce reaction values resulting from one or more reactions . . . detector 11 using bichromatic microplate reader.”; col. 6, line 14 – col. 7, line 34: discussing probability distributions.

Applicants have amended claims 81 and 82 to add the term “and.”

Applicants have also added new claims 116-118. Support for these claims may be

¹ For the Examiner’s convenience, reference is made to column and line numbers in parent application US 5,762,876.

found in the previously pending claim set, as well as in the aforementioned passages.

In view of these amendments, Applicants respond as follows:

1. Accompanying Information Disclosure Statement

With this Amendment and Response, Applicants submit an Information Disclosure Statement and copies of the substantive communications from the European Opposition Proceeding and Appeal Proceeding in a related family member application. Applicants' present claims are similar to those that were considered and approved by the Opposition Division of the European Patent Office. (See Item (5) on accompanying Form PTO/SB/08a at Annex 7) Although the EPO decision is not binding on the USPTO, Applicants offer the submission from that proceeding for the Examiner's consideration.

In paragraph 51 of the March 7, 2006 decision (see Item (5) on accompanying Form PTO/SB/08a), the EPO confronted an issue that is analogous to one of the issues presented below: whether analysis of genetic sequences based on size differences renders obvious Applicants' new claim 75 limitation "wherein each allele is a single specific nucleotide." The EPO noted that the primary cited reference before it, the Galbraith reference (D3), discussed the analysis of restriction fragments. Similarly, in the present case Kimpton discusses the analysis of a primer that had been extended by different numbers of bases. Neither Galbraith before the EPO nor Kimpton focuses on single specific nucleotides. One of the points made by the EPO was the inability of Galbraith to detect the change of one nucleotide. Applicants respectfully request that the Examiner consider the reasoning of the EPO when reconsidering whether Kimpton is applicable to the pending claims.

Additionally, in paragraph 51.3, the EPO considered whether the disclosure of a number of statistical techniques rendered obvious their application to the Applicants' claimed methodology. The EPO concluded that because there was no hint that any one of the disclosed statistical techniques were suited for the analysis of alleles which are single specific nucleotides, there was no basis for deeming the claims obvious. Likewise, Ledwina and Jeanpierre, relied upon in the pending Office Action, analyze available

information about genotypes and are not suited for the analysis of alleles. Applicants respectfully request that the Examiner consider that reasoning of the EPO when reconsidering whether either to combine Ledwina and Jeanpierre with Kimpton or to conclude that the combined references render the pending claims obvious.

2. Response to Refusal to Recognize Priority Claim

The Examiner refused to recognize Applicants' claim of priority to applications 08/173,173; 07/775,786 and 07/664,837. Because Applicants do not herein try to disqualify any of the cited references as prior art based on the claimed priority, Applicants do not address the issue of priority at this time. However, Applicants reserve the right to demonstrate at a later time that they are entitled to a priority date earlier than that recognized by the Examiner.

3. Response to Rejection of Claims 75-76, 78-82, 85, 86, 91-93, 95, 96-98, 102, 106-109, and 112-115

The Examiner rejected claims 75-76, 78-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and 112-115 under 35 U.S.C. § 103(a) as being unpatentable over Kimpton in view of Ledwina and Jeanpierre. Applicants' previously filed claim sets have been rejected based on this combination of references in prior Office Actions. However, Applicants submit that in view of the amendments above: (a) the cited references would not in combination disclose Applicants' currently claimed invention; and (b) a person of ordinary skill would not combine these references in the manner in which the Examiner combined them.

a. The references do not disclose the limitations of the claims

Applicants submit that the pending claims are patentable over the art of record, because the references do not, either alone or in combination show at least the following five limitations that are common to the claims: (1) in Step E: "determining the genotype . . . wherein each allele is a single specific nucleotide"; (2) in Step A: "reacting the

material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus, wherein the first reaction value is the intensity of an allele-specific quantitative signal”; (3) in Step C: “establishing a distribution set of probability distributions, including at least one distribution, associating hypothetical reaction value intensities with corresponding probabilities for each genotype of interest at the locus”; (4) in Step D: “applying the first reaction value to each pertinent probability distribution to determine a measure of the conditional probability of each genotype of interest at the locus, wherein the conditional probability is a measure of the likelihood of the genotype given the first reaction value”; and (5) in Step E: “determining the genotype of said subject based on the data obtained from step (D).”

First, none of the cited references disclose or suggest determining a genotype wherein each allele is a single nucleotide. Indeed, Kimpton cannot determine a genotype wherein each allele is a single nucleotide. Kimpton is directed to developing a method to fingerprint individuals through their STRs. In order to do this, he analyzes variations within a population by focusing on STRs that are at least three nucleotides in length. (Kimpton, p. 13 tri and tetrameric repeats) Kimpton’s focus on STRs that are at least three nucleotides long is necessary because of an inability to reliably discriminate between oligonucleotides that differ in size by fewer than three bases.

Ledwina also fails to disclose a method of determining a genotype wherein each allele is a single nucleotide. Ledwina is directed to characterizing the admissible test for Hardy-Weinberg equilibrium. (Ledwina Abstract) Relevant here, Ledwina starts from the proposition that individual genotypes in a population are known and examines this information to determine whether it meets the test for Hardy-Weinberg equilibrium. (Ledwina, p161 defining gene frequencies) Therefore, Ledwina fails to disclose or suggest determining a genotype wherein each allele is a single nucleotide. The teaching of Ledwina applies *after* the step of determining the genotype as recited in step E of claim 75.

Jeanpierre also fails to disclose a method of determining a genotype wherein each allele is a single nucleotide. Jeanpierre is directed to a method for providing the

likelihood of a genotype on an unsampled individual when information about the genotype of the individual's relatives is known. (Jeanpierre Abstract) Jeanpierre does not mention the number of nucleotides in the allele that he analyzes. Instead, Jeanpierre focuses on examining known genotypes in a pedigree to predict the genotype of the unsampled individual. Thus, Jeanpierre starts from the proposition that genotypes of others in the individual's pedigree are known. Like Ledwina, the teaching of Jeanpierre applies *after* step E of claim 75.

Second, none of the cited references disclose or suggest measuring a reaction value that is "the intensity of an allele-specific quantitative signal," as recited in step A of claim 75. Kimpton examines STRs and measures a position on a gel after electrophoresis. (Kimpton p. 16 "Band sizes were generated automatically by comparison with a standard sizing ladder included in every sample prior to gel electrophoresis."). He accomplished this by labeling his primers (page 14 of Kimpton "primers were labeled"; page 16 of Kimpton "tagged by the attachment of a fluorescent dye molecule to one of each pair of locus specific primers"), observing the distance migrated and using gel electrophoresis. Because the primers would all have the same type of label, he did not measure the "intensity of an allele-specific quantitative signal," and instead measured the distance and size. Had he focused on the intensity of the label on the primer and not the migration on the gel, he would not have generated results of any use because he would not have been able to differentiate sizes and sequences – sequence extensions would have no correlation to signal intensity.

Ledwina does not disclose any reactions, obtain any reaction values or focus on reaction values that are indicative of signal intensities. Ledwina addresses the issue of determining whether genotype information of a plurality of individuals is indicative of Hardy-Weinberg equilibrium. (Ledwina Abstract) Thus, whereas Applicants' step A focuses on obtaining the micro information that is probative of a specific individuals' genotype, Ledwina assumes that this information (the genotype) is already known and aggregated for a plurality of individuals and asks the macro question of whether the aggregate of genotypes is indicative of population equilibrium.

Jeanpierre, like Ledwina, does not concern itself with experimentally obtaining information from a biological sample of a subject. Therefore, there is no suggestion of obtaining a reaction value that is indicative of the intensity of an allele-specific quantitative signal. In fact, Jeanpierre suggests a method that may be of use precisely when there is no access to a biological sample that contains the genetic material of interest. (See Jeanpierre Summary p. 325 “The likelihood of a genotype of an unsampled individual.”) Thus, it teaches away from Applicants’ invention.

Third, none of the references disclose or suggest establishing a set of probability distributions in which hypothetical reaction value intensities are associated with corresponding genotypes as claimed in step C of claim 75. As the Examiner notes, Kimpton does not suggest this step. (See page 6 of February 21, 2008 Office Action)

Ledwina similarly does not suggest step C. As noted above, Ledwina assumes that all individual genotypes in a population are known. It starts from the proposition that someone somehow has correctly collected the genotypes of a plurality of persons. This information is then examined to determine whether it is indicative of Hardy-Weinberg equilibrium. Thus, Ledwina cannot suggest associating hypothetical reaction values of experimental testing with a probability of a specific genotype. To do so would be inconsistent with the goal of Ledwina, which is to consider the admissibility of population data, not to do as Applicants have done, to focus on the informational value of individual testing data.

Jeanpierre similarly does not suggest associating hypothetical reaction value intensities with the probabilities of a genotype. Instead, Jeanpierre focuses on associating familial genetic data with the probability of a genotype of an unsampled individual.

Fourth, none of the references disclose or suggest measuring the conditional probability of a genotype of interest by applying an experimentally derived reaction value to probability distributions as reflected in step D of claim 75. As the Examiner notes, Kimpton does not concern itself with conditional probability. (See page 6 of February 21, 2008 Office Action.)

Ledwina is also distinct from the claimed limitation. Ledwina, although

referencing conditional probabilities, focuses on “conditional probability distribution” with respect to a population. When discussing conditional probability, it is important to distinguish two parameters: (i) what is the condition precedent – the variable that is given or provided; and (ii) what is the outcome or conclusion of which one seeks to know the likelihood. Neither of these parameters are the same in Ledwina and the claimed invention. With respect to (i), Ledwina starts with an already known aggregate genotype of a population, whereas Applicants’ claimed method starts with a reaction value, which is the intensity of an allele-specific quantitative signal, from a biological sample of an individual. With respect to parameter (ii), Ledwina seeks to know the likelihood that the information of (i) is suggestive that a population meets Hardy-Weinberg equilibrium, whereas, step D of Applicants’ claimed method seeks to know the likelihood that an individual possesses a specific genotype. These differences are critical with respect to both timing and scale. Ledwina starts with genotype information, while Applicants’ method seeks to determine genotype information. Therefore, Ledwina fails to disclose or suggest the limitation of step D.

Similarly, Jeanpierre does not suggest applying reaction values in the context of conditional probability because as noted above Jeanpierre is limited to the situation in which reaction values for the genotype of the individual of interest are unavailable.

Fifth, none of the references disclose or suggest determining the genotype of a subject based on the data obtained from the determination of the measure of conditional probability. Kimpton does not disclose the use of a conditional probability to determine a genotype. Instead, Kimpton determines the genotype based on band sizes generated by comparison with a standard sizing ladder. (See Kimpton at p. 16)

Ledwina does not determine the genotype at all. Instead he examines an aggregate of known genotypes and determines whether it meets the Hardy-Weinberg equilibrium. Jeanpierre does determine a genotype, but the genotype is not based on the conditional probability that is considered for the experimentally derived reaction value. Instead, Jeanpierre bases its determination on genotypes of others in an individual’s pedigree.

Because none of the three cited references disclose the five aforementioned limitations, those references do not, alone or in combination, render the claims obvious.

b. The references were improperly combined

Applicants submit that the Examiner incorrectly combined the aforementioned references. They are directed to different problems and offer different and mutually exclusive solutions. Kimpton is directed to developing a method by which to fingerprint individuals through their STRs; thus, Kimpton seeks to address not what a specific gene is, but rather whether there is a genetic match between two samples. Ledwina addresses the issue of determining whether genotype information of a plurality of individuals is indicative of Hardy-Weinberg equilibrium; not what is the genotyping of any particular individual. And Jeanpierre is directed to determining the genotype of an individual when that individual has not himself been the subject of a genetic test. Applicants explain in more detail below why these references should not have been combined.

Kimpton examines multiple STR regions in order to solve the problem of human identity. Because so many people have the same number of STRs at any given locus, Kimpton must simultaneously focus on different regions of the genome and run tests on individuals to profile them. Ledwina is not concerned with human identity or the genotype of any one individual. Instead, he is concerned with a distribution of genotypes within a population. Thus, whereas in Kimpton the unknown is an individual's identity as against all other persons on the planet, in Ledwina, the unknown is the hypothetical distribution of the same alleles across a population as hypothesized by Hardy-Weinberg. Because of these fundamental differences, there is no rationale for combining Kimpton, which was directed to finding a way to profile based on each individual's unique genetic make-up, with Ledwina, which is only applicable with respect to information that is not unique to each person and instead is distributed throughout the population.

Similarly, a person would not look to combine Jeanpierre with Kimpton, because Jeanpierre has the limited applicability to when the individual whose genotype is of

interest is not available, whereas in Kimpton that person's genotype must be empirically tested. Moreover, whereas Jeanpierre is directed to making use of the fact that there are a finite number of genotypes for a given locus in order to better determine the genotype of a subject, Kimpton seeks to take advantage of the almost infinite number of genetic profiles that exist in order to distinguish each individual from every other individual. Because these references focus on and require such different systems in which to conduct analyses, a person of ordinary skill in the art would not combine them.

Finally, one would not combine Jeanpierre with Ledwina because whereas Ledwina is concerned only with the distribution of genotypes among a population Jeanpierre can only offer a better estimate of the probability of a genotype of an individual by ignoring population statistics and focusing on the known genotypes of family members.

Based on the foregoing Applicants submit that claim 75 is patentable over the art of record. All of the remaining previously rejected claims depend either directly or indirectly on claim 75. Accordingly, they are patentable over the art of record as well.

4. Response to Rejection of Claims 75-82, 85-87, 91-98, 100, 102, 106-115

The Examiner rejected claims 75-82, 85-87, 91-98, 100, 102 and 106-115 under 35 U.S.C. § 103(a) as being unpatentable over Kimpton in view of Ledwina and further as motivated in view of Jeanpierre and further in view of Goelet. The Examiner cited the additional reference for this basis of rejection for its teaching of genetic bit analysis methods, single specific nucleotide alleles and the association of a mutation with a restriction site.

Applicants respectfully submit that Goelet does not disclose at least the following three limitations of claim 75, all of which are as noted above also not disclosed in Kimpton, Ledwina or Jeanpierre: (1) in Step C: "establishing a distribution set of probability distributions, including at least one distribution, associating hypothetical reaction value intensities with corresponding probabilities for each genotype of interest at the locus"; (2) in Step D: "applying the first reaction value to each pertinent probability

distribution to determine a measure of the conditional probability of each genotype of interest at the locus, wherein the conditional probability is a measure of the likelihood of the genotype given the first reaction value”; and (3) in Step E: “determining the genotype of said subject based on the data obtained from step (D).”

Goelet discloses a method of analyzing an allele that is a single nucleotide. Goelet is directed to nucleic acid genotyping by polymerase extension of oligonucleotides using labeled terminators. He exposes a template nucleic acid to a primer and labeled terminators. If the label is detected in the extended primer, then Goelet concludes that the target contains the complementary nucleotide at an interrogation site. (Goelet p. 24) As the examples in Goelet show, Goelet assumed that his experimental results were correct and did not consider the accuracy or probability that they were correct. (Goelet pp. 37 – 47) Therefore, Goelet does not suggest any of the three aforementioned features of the pending claims, all of which are directed to using and applying probability and statistics. Because as noted above, none of the other cited references disclose these features, the rejection should be withdrawn.

Also, Goelet does not provide a suggestion for the combination of Kimpton, Ledwina or Jeanpierre with each other. Moreover, there is no rationale for combining Kimpton and Goelet. Goelet analyzes an allele that is a single nucleotide, and, as discussed in section 3, Kimpton is not suited to determine a genotype where each allele is a single nucleotide. Therefore, for the reasons described above in section (4)(b), even if the references did in combination disclose all of the recited features of the claims, the rejection should be withdrawn because their combination was improper.

5. Request for Interview

Applicants request that the Examiner grant a telephonic interview to discuss this Amendment and Response. Applicants propose November 6, 2008 at 1 pm. At the interview will be the undersigned attorney of record, Scott D. Locke, as well as persons from Beckman Coulter, the assignee of record. If the proposed time and date is not

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acceptable, Applicants request that the Examiner notify the undersigned attorney of record so that another time and date may be proposed.

If any fees are due other than the enclosed fee for the petition for extension of time, please charge, Deposit Account No. 11-0171 for such sum.

Respectfully submitted,

/Scott D. Locke/

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